Anti-IgE and Other Antibody Targets in Asthma

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Abstract Asthma is a heterogeneous disorder of unknown etiology that manifests as recurrent episodes of coughing, wheezing, and breathlessness. These symptoms are often debilitating and exacerbations usually are unexpected, resulting in work

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Y. Chernajovsky, A. Nissim (eds.) *Therapeutic Antibodies. Handbook of Experimental Pharmacology 181.*

or school absences, limitations in activity, reduced quality of life, and personal and economic hardships.

Over the past several decades, a great deal has been learned about asthma pathophysiology, and currently available therapies have revolutionized asthma treatment. However, asthma remains a global public health problem, and the hope is that newer therapies targeting specific biological mediators of asthma, particularly antibody-mediated therapies, offer exciting new modes to the control of this disease. We will review some of these therapies, with the majority of attention devoted to anti-IgE therapy which has been approved for treatment of adult and childhood asthma by the US Food and Drug Administration (FDA) since 2003.

1 Asthma Background

1.1 Asthma Epidemiology

Roughly 17 million Americans are affected by asthma, one-third of whom are children (Gold and Wright 2005). Worldwide estimates of asthma prevalence range from 2 to 36% of various international populations (Braman 2006). Currently, the incidence and prevalence of asthma in the US population overall appears to have reached a plateau, but there may well be increases within certain racial and ethnic groups (Cohen et al. 2006; Lugogo and Kraft 2006). Many patients with asthma also make frequent visits to their ambulatory care provider or the emergency department. There has been a recent increase in the rates of outpatient and emergency room visits from 1980 to 1999 as reported in the Morbidity and Mortality Weekly Report (Mannino et al. 2000), indicating that asthma control is suboptimal in the US population. Hospitalizations for asthma are a significant factor in asthma-related cost. Patient absenteeism from work likely also has an important impact on productivity. Thus, asthma remains an important public health problem both nationally and globally (Eder et al. 2006).

1.2 The Biology of Asthma

Over the last several decades, much has been learned about asthma physiology and pathogenesis. For decades, the paradigm was relatively simple: exposure from an environmental allergen in a susceptible host resulted in inflammation in the airways; the inflammation was then felt to result in the symptoms of the disease. However, what became increasingly clear is that the symptoms of the disease and the asthma clinical severity were only loosely connected in many individuals with asthma. Today, a number of cells and molecular determinants were felt to play important roles in asthma pathogenesis. Our current understanding is that the immunopathology of asthma is complex and involves a dynamic interplay among various components of the adaptive and innate immune systems, the environment, and host

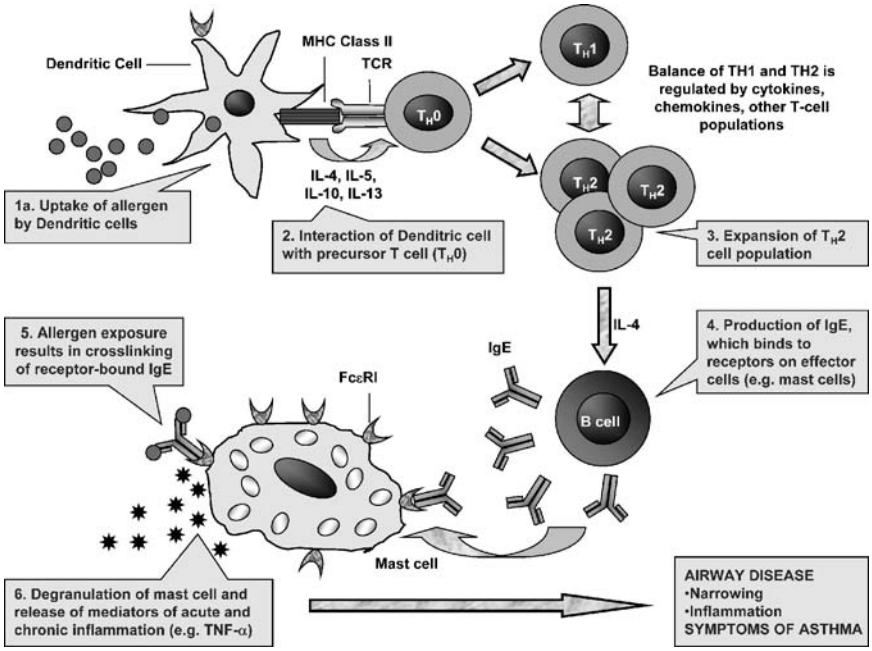

Fig. 1 Classical mechanisms of allergic asthma. Allergens are taken up by dendritic cells and presented to T cells. The T-cell response is balanced between the T_H1 and T_H2 response, and this interaction is balanced by numerous other factors. The T_H2 response classically results in clonal expansion of the T_H2 cell population, which manifests by activation of B lymphocytes. These activated B cells transform and produce allergen-specific IgE, which then binds to the FcεRI receptor on effector cells (e.g., mast cells, basophils). Crosslinking of allergen to receptor-bound IgE results in degranulation and subsequent release of numerous inflammatory mediators. The resulting acute and chronic inflammation results in airway disease and the symptoms of asthma

susceptibility. Certain factors may modify these effects to result in overt clinical disease, and subclinical disease may progress despite excellent therapy targeted against asthma.

The classical paradigm of asthma is depicted in Fig. 1. After a dendritic cell or other antigen-presenting cell encounters an allergen, the cell triggers the naive T cell population to undergo a specific clonal expansion. Through numerous complex mechanisms which involve isotype class switching, this T_H2-mediated reaction results in the production of B cells which secrete allergen-specific immunoglobulin E (IgE). These IgE molecules have the ability to bind to receptors on effector cells such as mast cells. On subsequent allergen re-exposure, the allergen, IgE molecules, and FcεRI receptor interact to result in mast cell degranulation, the release of numerous inflammatory mediators, and the subsequent symptoms of asthma. Within this paradigm, antibody targets that inhibit important mediators and effectors appear particularly promising for the treatment of asthma and other allergic diseases. To date,

these therapies generally center on the adaptive immune system and its production of immunoglubilins (e.g., IgE) and cytokines (e.g., TNF-α) that are felt to drive many of the mechanisms of asthma. We will review a few of these potentially therapeutic antibodies in detail below.

1.3 Current Treatments for Asthma

Numerous guidelines for the diagnosis and treatment of asthma have been published since the 1980s. In the United States, in 1991, the National Heart, Lung, and Blood Institute (NHLBI) published its first set of guidelines (NHLBI 1991), which were subsequently updated by the National Asthma Education and Prevention Program in 1997 (NAEEP 1997) and again in 2002 (NAEEP 2002). The most famous of the global guidelines were originally published by the Global Initiative for Asthma (GINA) (NHLBI/WHO 2002), a joint consortium of the NHLBI and the World Health Organization that updates its guidelines at least annually. A recent update of the GINA guidelines was just released in 2006, with new NHLBI guidelines expected in 2007. Updated guidelines can be found on the GINA website (http://www.ginasthma.com/).

Essentially, the treatment of asthma centers around the control of or response to patient symptomatology with particular attention to symptoms of dyspnea, cough, and wheezing. Therefore, patient well-being, number and severity of exacerbations, and improvement in quality of life (e.g., fewer missed days of work/school) are the most common assessments of response to treatment. Treatment effectiveness may also be objectively quantified by physiological measurements such as measures of pulmonary function. Common physiological parameters include peak expiratory flow rate (PEF) with forced exhalation as well as the forced expiratory lung volume in 1 s (FEV1); both may be reduced from baseline during disease flares, but the results are not consistent among or within cohorts of asthmatics. Notably, the actual airway inflammation and remodeling that ensue are not well-measured by current methodologies. There has been some excitement recently about using quantitative measurements of exhaled nitric oxide as a surrogate marker for airway inflammation, but this has not been universally accepted nor available. Therefore, symptoms and patient tolerance dictate current guidelines to asthma treatment, also reflecting a shift toward improving or maintaining symptom control rather than trying to alter disease severity. Importantly, the newer asthma treatment guidelines represent a shift in thought from categories of asthma severity to categories of control, regardless of severity. Therapy is stepped up or down depending on overall control.

Available therapies are generally divided into nonpharmacologic and pharmacologic categories. Nonpharmacologic therapies in asthma center around avoidance of asthma triggers. Triggers may be discrete allergens for which the patient has a known allergic predisposition (e.g., a positive skin-prick test on skin testing). For example, certain species of house dust mite are known environmental allergens, and many experts recommend that patients cover their mattresses with plastic covers so

as to avoid direct exposure to as much house dust mite antigen as possible. Avoidance of the offending allergen makes intuitive sense, but many of the allergens are ubiquitous in the environment, difficult to avoid, or difficult to determine. Other nonallergen triggers include exposure to environmental tobacco smoke, cold air, and exercise, none of which may be easy to avoid. Clearly, trigger avoidance, though of great importance, is markedly insufficient as sole therapy for the majority of asthmatics.

The mainstays of pharmacological therapies for asthma have been bronchodilators and corticosteroids. Bronchodilators, particularly β-agonists, dilate the small airways and can have short or long-lasting effects, depending on the formulation. These are not generally thought to treat the underlying inflammation, but rather provide symptomatic relief. Given that the hallmark of allergic asthma is inflammation, the underlying inflammation of acute and chronic asthma is treated with corticosteroids. Corticosteroids decrease inflammation through numerous proposed mechanisms, and to date oral or parentally administered corticosteroids are the mainstay of treatment for patients with severe asthma, especially during a flare requiring hospitalization. The major advance in asthma pharmacotherapy in the last two decades has been the introduction and widespread use of inhaled corticosteroids in patients with mild to moderate asthma. Though they are generally well-tolerated, inhaled corticosteroids have potential adverse effects. These have usually been thought to be mild and easily treatable (e.g., throat pain, oral thrush), but recent evidence suggests that inhaled corticosteroids reach the systemic circulation and may have untoward effects on bone growth and suppression of the hypothalamic–pituitary axis leading to possible adrenal gland dysfunction and osteoporosis (Gulliver and Eid 2005). Moreover, the combination of inhaled corticosteroids and long-acting β-agonists may be insufficient to treat patients with severe asthma. It is being increasingly recognized that a small number of patients, generally those with severe persistent asthma, are the most difficult to treat and are responsible for a large segment of the costs of asthma (Dolan et al. 2004). These patients demonstrate a need for additional therapeutic options to achieve enhanced asthma control.

Second-line agents for the control of asthma, such as mast-cell stabilizing agents, leukotriene inhibitors and methylxanthines, have variable roles in the daily management of asthma. Desensitization immunization with antigens (allergens), which is used mainly in the United States for allergic rhinitis, is not effective for the majority of asthma patients. Overall, these therapies have benefited subsets of patients; therefore, new therapeutic targets are needed. Many of these therapies are targeted toward specific aspects of the innate and adaptive immune response. More recently, the approval and use of anti-IgE antibodies has generated much excitement, as has the potential uses of other antibodies targeting asthma mediators. We will review the pathophysiology, mechanisms, and pharmacologic considerations of the latter agents in detail in this chapter.

2 Anti-IgE Antibodies for Asthma

2.1 Role of Immunoglobulin E in Asthma Pathogenesis

Immunoglobulin E (IgE) has been known to be a key mediator of asthma and other allergic disorders for over 30 years and plays a central role in allergic responses to allergens in patients with asthma and rhinitis. IgE was officially recognized by the WHO as a new immunoglobulin in 1968. Its receptor was first identified in 1974 (Kulczycki et al. 1974) while more detail on the receptor's molecular weight and valence was published in 1977. After further characterization over the ensuing decades, Kinet identified the IgE-mast cell interaction as a paradigm for the antigen–antibody relationship. Current evidence suggests that the majority of asthma has an allergic basis (Holt et al. 1999), and that IgE is central to the initiation of both allergic and nonallergic asthma. Elevated serum levels of specific IgE toward common environmental allergens characterize allergic diseases such as asthma and rhinitis as illustrated by several lines of evidence. Elevated serum IgE in the first year of life, IgE sensitization, and exposure to airborne allergens are all risk factors for the development of childhood and lifelong asthma (Sporik et al. 1990; Martinez et al. 1995). Concordantly, increased IgE levels are associated with increasing asthma disease severity in patients with moderate to severe persistent asthma (Borish et al. 2005). This is conceptually supported by the correlation of elevated serum IgE with sputum eosinophilia (Covar et al. 2004) and elevated levels of nitric oxide in airways of asthmatics (Strunk et al. 2003).

IgE is produced by B cells after sensitization and has a short half-life. Despite low serum concentrations, IgE is immunologically highly active due to the large number of high-affinity IgE receptors on mast cells and basophils. In addition, IgE upregulates receptors on several cell type, including basophils and mast cells. The binding of IgE to the receptors on these cells results in the formation of cross-links between the allergen and the IgE molecule, thereby initiating an inflammatory cascade through release of a variety of mediators, including histamine, prostaglandins, leukotrienes, chemokines, and platelet-activating factor. In some individuals with allergic asthma, higher than normal IgE levels may increase persistent airway inflammation and bronchial hyperresponsiveness, presumably through ongoing chronic allergic activation of this complex system.

As in other antibodies, the antigen-binding site of IgE is contained in the Fab fragment. The Cε3 domains of the Fc fragment bind either of the two known IgE receptors, the high-affinity receptor (FCεRI) or the low-affinity receptor (FCεRII) (Buhl 2004). Importantly, the IgE-mediated allergic cascade involves a biphasic response with an immediate or early allergic response and a late allergic response (Dolovich et al. 1973). The early response occurs acutely, usually within 1 h of exposure to allergen, whereas the late response occurs 4–24 h later. IgE plays a critical role in both the early and late phase responses via interaction with the FcεRI and FcεRII receptors.

The early allergic response results from IgE-mediated mast cell degranulation. Interaction of receptor-bound IgE antibodies with soluble multivalent allergen leads to receptor aggregation (Bradding et al. 2006). By signal transduction, a complex series of events ensues culminating in rapid degranulation and release of the stored contents of cytoplasmic granules and newly formed mediators. Acute allergic symptoms are generated by interaction of these receptor mediators with specific receptors on target tissues; clinically, this cascade results in bronchospasm or acute asthma. Moreover, the severity of this response likely has a great deal to do with the mast cell density in the airways (Bradding et al. 2006). Disruption of the initial binding of IgE antibodies, thereby preventing activation of mast cells and other airway effector cells, is an important potential mechanism by which anti-IgE antibodies may attenuate the early allergic response.

Continued expression of mediators elicits an inflammatory response designated as the late-phase reaction, though the precise cause and significance of this late phase are less well understood. Eosinophils likely play a role, and in response to IgE binding to the FcεRI receptor, eosinophilic cytoplasmic granules and a number of cytokines and lipid mediators are synthesized and released by degranulation. However, the low level of FcεRI expression on eosinophils means this may not be the major pathway in the late phase response (Prussin and Metcalfe 2006). Given that IgE also enhances antigen presentation to T cells via FcεRI receptors on antigen-presenting cells (Maurer et al. 1995), this may explain the pathogenesis for the role of IgE in the late-phase response. Regardless of mechanism, this late phase response results in persistent symptoms, airway hyperresponsiveness, and bronchospasm (Strunk and Bloomberg 2006).

Additional effects of IgE and its binding to the FcεRII receptor are not fully understood but are being investigated heavily. Importantly, the expression of FcεRI in basophils correlates with serum IgE levels (Malveaux et al. 1978), suggesting that lowering IgE levels may attenuate the early asthmatic reaction. In turn, IgE can also directly or indirectly maintain the mast cell pool by protecting the cell from apoptosis (Kitaura et al. 2003), thereby proposing a mechanism whereby continued suppression of IgE may lead to persistent attenuation of allergic asthma symptoms. It is also likely that IgE may facilitate sensitization to allergens via effects on different cell types. For example, asthmatic airway smooth muscle expresses surface FcεRII and expression is upregulated by IgE-FcεRII binding (Hakonarson et al. 1999), so FcεRII may be involved in transepithelial migration (Buhl 2004). FcεRII is also implicated in the IgE-mediated presentation of allergen to antigen-presenting cells, and allergen presentation to T cells is enhanced by IgE-FcεRI complexes on antigen-presenting cells (Maurer et al. 1995). This allergen presentation leads to classic Th2 cell-mediated allergic reactions with resulting inflammation. Also after allergen inhalation, the number of dendritic cells recruited to the airway epithelia is increased in asthma, and the expression of FcεRI by these cells is also significantly increased compared to controls (Geiger et al. 2000). Allergens can thus be internalized and presented to dendritic cells via cross-linking of allergen-IgE antibodies bound to the alpha chain of FcεRI (Upham 2003). In regard to B cells, IgeE binds to FcεRII receptors on B cells, where it alters differentiation and regulation of

further IgE synthesis (Broide 2001; Oettgen and Geha 2001). In summary, the IgE molecule probably plays a number of unique roles in the allergic response, many of which require further elucidation.

2.2 *Anti-IgE as a Therapeutic Strategy*

Given the above clinical, epidemiologic, and biological evidence indicating the role of IgE in asthma pathogenesis, it is not surprising that anti-IgE therapies have been developed to treat allergic asthma and related disorders. The rationale for this was first published by Chang in 1987, who proposed that chimeric or humanized anti-IgE antibodies with a set of unique binding properties could be used for the isotype-specific control of IgE, and thus would be a logical therapeutic approach to IgE-mediated diseases (Chang 2000). IgE binding to its Fc receptors mediates both FecRI-mediated mast cell degranulation and FcεRII-mediated enhancement of

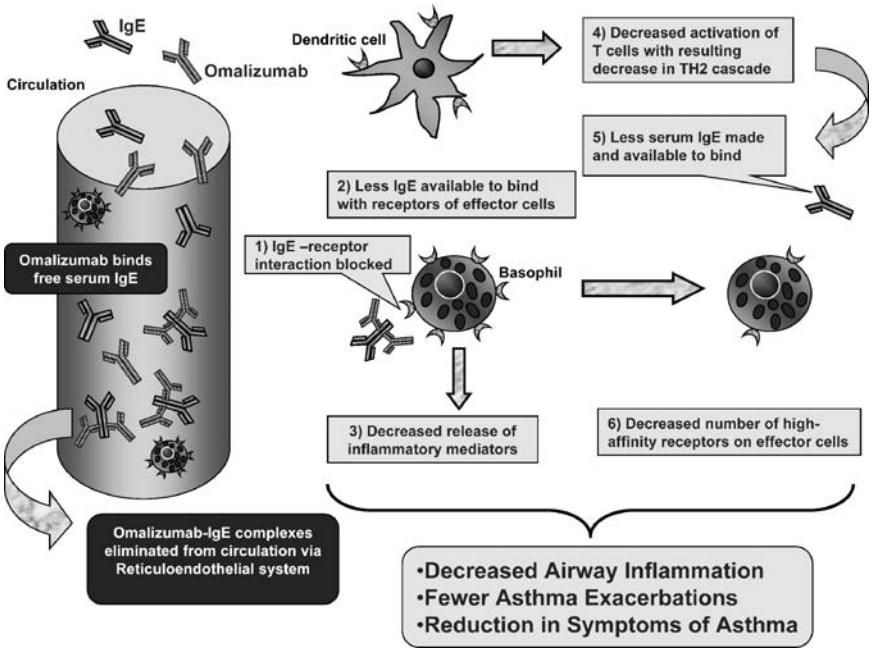

Fig. 2 Mechanisms of action of omalizumab. Omalizumab binds free IgE to form omalizumab-IgE complexes. The binding of omalizumab to the Fc portion of the IgE molecule: (1) prevents the binding of IgE with the high-affinity receptors of effector cells, including basophils, dendritic cells, and mast cells; (2) since these complexes are eliminated, there is then less free IgE available for the remaining receptors; (3) there is a resulting decreased release in inflammatory mediators; (4) a decrease in the allergic cascade results in fewer T_H cell reactions resulting in (5) less serum IgE being produced. (6) downregulation of high-affinity receptors on effector cells. The net effect then of omalizumab is decreased airway inflammation, fewer exacerbations, and a reduction in asthmatic symptoms

antigen presentation in the allergic reaction; both roles thus make anti-IgE therapy a potentially ideal target. A monoclonal anti-IgE antibody that binds free but not receptor-bound IgE would therefore be postulated to inhibit the initiation of the allergic cascade by preventing IgE binding to receptors.

The potential downstream effects of blocking IgE receptor binding are numerous. Blocking IgE binding to FcεRI receptors on dendritic cells could reduce the efficiency of antigen presentation to T cells, whereas blocking binding to those on mast cells and basophils could prevent allergen-induced degranulation and the release of inflammatory mediators (Fig. 2). It then becomes logical that if the inflammatory mediators are not released, the progression of an asthmatic reaction would be attenuated and a patient's symptoms improved. Moreover, if new immune cells such as basophils are created to replenish the patient's systemic supply during routine cell turnover, these new cells would not have gone through upregulation of their FcεRI receptors because of the low plasma free IgE concentration (Chang 2000). As discussed later, this latter effect may explain why anti-IgE therapy takes several weeks to achieve maximal benefit.

2.3 The Development of Anti-IgE Antibodies and the Emergence of Omalizumab (Xolair^{TM})

As intriguing as the prospect is for an anti-IgE monoclonal antibody, there are a number of considerations involved in the development of therapeutic monoclonal antibodies. First of all, the antibody must be nonimmunogenic and nonaphylactogenic, issues which hindered the development of murine monoclonal antibodies for decades (Dillman 1989). Secondly, the binding of the therapeutic antibody to the IgE molecule should occur with a high degree of specificity and affinity. Moreover, the binding affinity between IgE and the antibody should favor the formation of immune complexes small enough to result in a reasonable degree of clearance without adverse reactions. Lastly, for therapeutic efficacy, a dose of anti-IgE capable of almost completely removing free IgE might be necessary, because only 2000 IgE molecules are required for half-maximal histamine release from basophils exposed to allergen (MacGlashan 1993).

Based on the above, two recombinant humanized monoclonal antibodies have been developed against the IgE molecule. The antibodies are made with a human IgG1 framework and a complementarity-determining region from a murine anti-IgE antibody (Presta et al. 1993). Overall, less than 5% of the amino acid residues are murine, which is why the molecules are considered to have low potential for immunogenicity. The antibodies recognize the Cε3 domain of free human IgE, the same Fc site as the high-affinity receptor binding site. Specifically, the FcεRI binding site within the Cε3 domain depends on six exposed amino acids localized in three loops: Arg408, Ser411, Lys414, Glu452, Arg465, and Met469 (Presta et al. 1994). When the IgE antibody binds to this region, the interaction between IgE and effector cells is blocked (Fig. 2). Moreover, the antibody-IgE complexes formed as a

result of treatment are small and not thought to be able to trigger complement activation nor give rise to immune complex-mediated pathology (Liu et al. 1995). Importantly, the antibodies only bind free IgE, not cell-surface-bound IgE. This ensures that there is no crosslinking of effector cells, and hence the effector cells are not activated. This may seem to be intuitively obvious, but has been an important challenge in the development of antibody-mediated therapies (Roskos et al. 2004). To test this concept, in vitro experiments have shown that anti-IgE did not induce histamine release from IgE-loaded human basophils (Shields et al. 1995).

Omalizumab (also referred to as rhu-Mab-E25, rhu-mab in the literature), is a recombinant humanized monoclonal antibody that was first cloned in 1992 by Genentech (Presta et al. 1993; Adis 2002). It was commercialized with Novartis and Tanox under the trade name Xolair. The second anti-IgE molecule developed is the CGP51901 or TNX-901 monoclonal antibody independently developed by Tanox (Chang 2000). The latter has been successfully used to treat subjects with peanut allergy in a phase II trial but is not yet commercially available (Leung et al. 2003). The two antibody development programs were combined in 1996, which targeted omalizumab for further development. Therefore, the vast majority of medical literature on clinical and biological data regarding anti-IgE therapies is based on omalizumab. As detailed later, omalizumab has been shown to reduce serum concentrations of free IgE, resulting in significant reductions in early and late asthmatic responses following allergen inhalation and improved asthma symptom control. In 2003, the FDA granted approval for the use of omalizumab in moderate to severe atopic asthmatic patients.

2.4 Pharmacokinetics and Dosing of Omalizumab

Developing a dosing regimen for omalizumab takes into account the pharmacokinetic properties and the goals of serum IgE reduction. Given subcutaneously, the drug is absorbed slowly, with an absolute bioavailability of 62%, and peak serum concentrations are reached 7–8 days following the injection (Genentech 2003). Interval of dosing is predicated on the long average terminal half-life of omalizumab of 19–22 days (Hochhaus et al. 2003). The serum concentration of total IgE in the nonatopic, nonasthmatic population is $<100\,\mathrm{IU\,ml^{-1}}$ ($<240\,\mathrm{ng\,ml^{-1}}$); however, in allergic individuals, this concentration varies from normal range to several hundred $\mathrm{IU\,ml^{-1}}$. Clinical benefit with omalizumab is observed when free IgE levels in serum are reduced to $50\,\mathrm{ng\,ml^{-1}}$ or less, but little additional benefit is gained with levels $<12\,\mathrm{ng\,ml^{-1}}$ (Hochhaus et al. 2003). It was then determined that omalizumab must be given at molar excess of 15–20:1 relative to baseline total IgE to achieve such a reduction in free IgE (Casale et al. 1997). Therefore, the ability of omalizumab to reduce free IgE levels to less than 10% of pretreatment level depends on the dose and the patient's weight and baseline IgE level (Boulet et al. 1997; Hochhaus et al. 2003). A pooled analysis of two previous studies with 859 patients with asthma found that administration of the minimum dose calculated to achieve a mean free IgE level of $25\,\mathrm{ng\,ml^{-1}}$ resulted in free IgE levels of $<50\,\mathrm{ng\,ml^{-1}}$ in more

Table 1 Dosing of Omalizumab

Pre-treatment serum IgE (IU ml^{-1})	Body Weight (kg)			
	30–60	>60–70	>70–90	>90–150
30–100	150 mg every 4 weeks	150 mg every 4 weeks	150 mg every 4 weeks	300 mg every 4 weeks
>100–200	300 mg every 4 weeks	300 mg every 4 weeks	300 mg every 4 weeks	225 mg every 2 weeks
>200–300	300 mg every 4 weeks	225 mg every 2 weeks	225 mg every 2 weeks	300 mg every 2 weeks
>300–400	225 mg every 2 weeks	225 mg every 2 weeks	300 mg every 2 weeks	Do not dose
>400–500	300 mg every 2 weeks	300 mg every 2 weeks	375 mg every 2 weeks	Do not dose
>500–600	300 mg every 2 weeks	375 mg every 2 weeks	Do not dose	Do not dose
>600–700	375 mg every 2 weeks	Do not dose	Do not dose	Do not dose

than 95% of patients (Hochhaus et al. 2003). As a footnote, there was no change in the serum IgE levels after inhalation of aerosolized omalizumab (Fahy et al. 1999), which leads one to suspect that the lack of efficacy of this route of administration may have somehow been due to its ineffectiveness at obtaining systemic levels.

Taking the above factors into account, an individualized tiered dosing table was developed to ensure that free IgE reduction is achieved (Hochhaus et al. 2003). The recommended dose is 0.016 mg per kilogram of body weight per international unit of IgE every four weeks, administered subcutaneously at either two-week or four-week intervals. The actual dose depends mainly on current body weight and pretreatment total IgE level; the corresponding dosing table (Table 1) takes into account the broad range of pretreatment total IgE levels and the patient body weights likely to be encountered in clinical practice. Patients requiring a monthly dose of $\leq$300 mg are treated once every 4 weeks while those requiring a higher dose receive two equal doses administered every 2 weeks. There is presently no recommended dose for patients with body weight greater than 150 kg and/or total IgE 700 IU ml^{-1} or greater.

The tiered dosing strategy has proven overall to be successful in meeting the targeted objectives. Results from large, placebo-controlled phase III clinical studies in patients with moderate-to-severe allergic asthma show overall consistent suppression of free IgE, with median serum free IgE levels well below the target of 25 ng ml^{-1} (10.4 IU ml^{-1}) across the omalizumab dose range (Busse et al. 2001; Milgrom et al. 2001; Soler et al. 2001). The clinical effectiveness of this strategy is detailed later in this chapter, but overall, the results indicate improved asthma symptom control in subjects with allergic asthma. Moreover, a retrospective pooled analysis of two of these studies was conducted to study the range of individualized doses and free IgE suppression in relation to clinical effectiveness. This analysis showed no additional clinical benefit at higher omalizumab doses or at serum free IgE levels lower than the average target of 25 ng ml^{-1} (10.4 IU ml^{-1}) (Hochhaus

et al. 2003). However, this latter aspect is controversial as others argue that higher dosing, particularly to achieve near-saturation of high-affinity receptors, has been poorly studied and may be of direct clinical benefit.

Biologically, following either intravenous or subcutaneous injection of omalizumab, a substantial reduction in the free serum IgE concentrations was demonstrated after a single injection (Casale et al. 1997). Notably, the magnitude of reduction was typically 89–99% from the pretreatment levels (Schulman 2001), and that this effect occurred regardless of different dosing regimens. Low levels of free serum IgE appeared to be sustained throughout the trials. Proof-of-concept studies have shown decreased numbers of eosinophils in sputum samples and bronchial biopsies (Djukanovic et al. 2004). Important studies have also shown a reduction in FcεRI receptor density on basophils, and a decrease in basophil responsiveness to stimulation by allergen of approximately 90% (MacGlashan et al. 1997). This indicates that FcεRI-receptor density is regulated by circulating levels of free IgE, and that reducing free IgE with omalizumab is very effective in decreasing FcεRI expression. Similar downregulation of FcεRI receptors has been noted with mast cells (Beck et al. 2004) and dendritic cells (Prussin et al. 2003), implying that the effector cell response to IgE is not only mediated by the IgE-FcεRI binding, but that the effects of IgE antagonism extend into later phases of the asthmatic response (Fig. 2). Concordantly, studies have shown decreased numbers of eosinophils in sputum samples and bronchial biopsies (Djukanovic et al. 2004), further supporting evidence that the underlying inflammatory response is being appropriately suppressed in asthmatic airways.

Additional considerations for dosing, beyond weight and pretreatment total IgE, do not appear to require dose adjustments. Specifically there is no need to adjust based on additional demographic factors such as age, gender, and ethnicity. There is also no need for adjustment based on renal impairment, as drug metabolism and elimination is via the reticulendothelial system of the liver and spleen. Though cases of hepatic and/or renal toxicity have not been reported, drug dosing in liver impairment has not been studied. Treatment duration itself is controversial. Bousquet and colleagues noted that, among patients who responded to 16 weeks' treatment with omalizumab, only 61% responded at 4 weeks whereas 87% had responded at 12 weeks (Bousquet et al. 2005). Although the mechanism of this delayed onset of action is unknown, it is likely that the downstream anti-inflammatory effects of anti-IgE activity require several weeks to achieve maximum efficacy. Therefore, a minimum duration of 12 weeks is currently recommended before determining the level of omalizumab response. Interestingly, after discontinuation of omalizumab therapy, changes in free IgE concentrations, basophil FcεRI expression, and allergen-induced histamine release from basophils slowly returned to pretreatment levels within 2–10 months (Saini et al. 1999). Based on this premise, some authors advocate treatment for years or possibly even lifelong (Chang 2000), but this concept is very controversial particularly in light of the high cost of omalizumab and unknown long-term risks associated with this medication.

2.5 Clinical Efficacy of Omalizumab

2.5.1 Overview

A number of phase II and III studies have been published to date on the effectiveness of omalizumab. Published studies to date have come from the United States, Europe, and Japan, with the majority of human subjects being adults with allergic asthma. Primary outcomes in the majority of studies included (1) a reduction or termination in steroid usage and (2) decreased frequency of exacerbations (as defined by either hospital admissions, emergency room visits, days lost from work/school, unscheduled doctor visits, and/or increase in medicine). Secondary outcomes varied in the studies, but generally included assessments of asthma symptoms, health-related quality of life indices, rescue medication usage, physiological measures of pulmonary function testing, and adverse events. The results of the above analyses have been pooled and recently published by the Cochrane Collaboration (Walker et al. 2006), which evaluated 3,143 subjects with mild to severe allergic asthma enrolled in 14 published and unpublished studies. Essentially, there have been key phase III clinical trials in 1651 patients (age, 6–76 years) (Busse et al. 2001; Milgrom et al. 2001; Soler et al. 2001; Holgate et al. 2004). Moreover, a number of other exploratory and secondary analyses have been performed to date and are summarized below.

2.5.2 Patient Selection and Study Design

In four randomized, double-blind, placebo-controlled trials (Busse et al. 2001; Milgrom et al. 2001; Soler et al. 2001; Holgate et al. 2004), patients had asthma for at least one year and required treatment with inhaled corticosteroids. All patients were nonsmokers and had at least one positive skin test to a perennial aeroallergen (specifically, dust mites, cockroaches, or dog and cat dander), as well as a serum IgE between 50–700 IU ml^{-1}. Each trial followed a similar overall structure: (1) after patient enrollment, a 4–10 week *run-in period* was used to optimize and stabilize current therapies including adjustments of inhaled corticosteroids; (2) a *stable-steroid phase* for 12–16 weeks during which inhaled corticosteroids were maintained at a stable dose, followed by (3) a *steroid-reduction phase* during which inhaled corticosteroids were lowered to the lowest range required for asthma control.

The majority of patients were adults with moderate to severe persistent asthma (requiring doses of inhaled beclomethasone, or its equivalent, ranging from 168 to 1200 mcg per day) (Strunk and Bloomberg 2006). Two of these trials included adolescents and adults (Busse et al. 2001; Soler et al. 2001), and one was a study of children 6–12 years of age (Milgrom et al. 1999b). The fourth trial evaluated patients with more severe asthma who required high-dose inhaled corticosteroids for symptom control (fluticasone, $\geq$ mcg per day) (Holgate et al. 2004). A more recent trial involved patients who required at least 1000 mcg per day of inhaled beclomethasone plus a long-acting bronchodilator for symptom control (Humbert et al. 2005). These issues are important, given that the use of first-line therapies

(i.e., inhaled corticosteroids) in these patients with asthma were surprisingly low, especially in the earlier trials. Since omalizumab is only FDA-approved as a second-line agent in the current treatment of asthma, it is very possible that studies may have had a biased effect toward efficacy if steroid doses were indeed not optimized prior to administration of omalizumab.

Omalizumab has been given via intravenous, subcutaneous, and inhalational routes. In asthmatic adults, both intravenous and subcutaneous routes were efficacious (Boulet et al. 1997; Fahy et al. 1997; Milgrom et al. 1999a; Busse et al. 2001; Soler et al. 2001; Holgate et al. 2004; Vignola et al. 2004), whereas the inhalation route showed no efficacy and did not reduce serum-free IgE (Fahy et al. 1999). Therefore, the subcutaneous route was selected as the most practical for clinical use, being used in the largest trials and subsequently receiving FDA approval.

2.5.3 Results

The results of the major clinical trials, as compiled by the Cochrane Collaboration and summarized in Table 2, are detailed below. When Omalizumab was used as an add-on therapy to inhaled or oral corticosteroids in patients with stable asthma, there seemed to be a significant reduction in the risk of asthma exacerbations, particularly in the severe asthma group (Busse et al. 2001). Moreover, the exacerbations appeared to be of lesser duration and severity. Also, patients treated with omalizumab were significantly more likely to be able to decrease the dose of inhaled corticosteroids, often decreasing dosage by greater than 50% or even being able to discontinue inhaled corticosteroids completely (Milgrom et al. 1999a; Busse et al. 2001; Soler et al. 2001). Interestingly, treatment with omalizumab was also associated with shorter duration of exacerbations in adults with moderate to severe asthma (Busse et al. 2001), but not in a pediatric subgroup (Lemanske et al. 2002). Concordantly, there was a reduction in β-2 agonist usage in adolescents and adults with moderate to severe asthma, both in the subcutaneous and high-dose IV formulations. In patients taking oral corticosteroids, there was not a significant difference in the number of patients being able to withdraw from oral steroid therapy between omalizumab and placebo treatment (Holgate et al. 2004).

Omalizumab reduced free IgE by 89–99% in asthmatic subjects (Walker et al. 2006), which indicates that the antibody is indeed binding to free IgE. Though this may intuitively seem adequate in its ability to suppress asthma symptoms, some authors suggest that this inability to reach 99% suppression of free IgE may reflect undertreatment in the clinical trials (Avila 2007). Therefore, it is conceivable that omalizumab may have greater efficacy than was demonstrated in the clinical trials.

The effects of omalizumab on lung function and airway hyperresponsiveness were small and did not reach statistical or clinical significance (Djukanovic et al. 2004). Only one published study showed statistically significant improvement in lung function as measured by the forced expiratory volume over 1 s (FEV1) (Vignola et al. 2004), with the magnitude of improvement being of dubious clinical significance. This lack of significant improvement is not surprising, given that other studies

Table 2 Clinical efficacy of omalizumab based on Cochrane Analysis (Avila 2007)

Clinical outcome	Superiority of Omalizumab vs. placebo
Reduction in free serum IgE (range)	89–99%
Odds ratio of having exacerbation	0.60 (95% CI 0.42–0.86)
Rate of exacerbations per subject	−0.18 (95% CI −0.10 to −0.25)
Duration of exacerbation	7.8 vs. 12.7 days ($p < 0.001$)
Rescue short-acting bronchodilator use	−0.63 puffs/day (95% CI −0.90 to −0.36)
Peak expiratory flow ($ml\,min^{-1}$)	$3.6\,ml\,min^{-1}$ (95% CI −23.5 to 160.1)
End of treatment FEV1 (ml)	68.3 ml (95% CI −23.5 to 160.1)
Change in FEV1 (ml)	73 ml ($p = 0.03$) or 2.8% ($p = 0.04$) better
End of treatment asthma symptom score change	−0.046 (95% CI −0.75 to −0.29)
Reduction in symptom score $\geq 50\%$	2.99 (95% CI 1.64–5.44)
Improvement in asthma quality-of-life scores	0.32 (95% CI 0.22–0.43)
Rate of subjects achieving asthma control	59% vs. 41% ($p < 0.001$)
Odds ratio of achieving good or excellent asthma control	2.6 (95% CI 1.9–3.4)
Odds ratio of complete inhaled corticosteroid withdrawal	2.5 (95% CI 2.0–3.1)
Rate of complete steroid withdrawal	34% vs. 14% ($p < 0.001$)
Inhaled corticosteroid reduction	−118 mcg BDP (95% CI −154 to −84)
Likelihood of reducing ICS $\geq 50\%$	2.5 (95% CI 2.0–3.1)
Odds ratio of withdrawing oral corticosteroid	1.18 (95% CI 0.53–2.63)
Median relative reduction in oral corticosteroid use	69% vs. 75% ($p = 0.68$)
Odds ratio of being hospitalized for asthma	0.11 (95% CI 0.93–0.48)
Number need to treat to:	**Number (95% CI)**
Prevent one exacerbation	11 (9–16)
Enable one patient to stop steroid therapy	6 (5–8)
Enable one patient to reduce steroid therapy by >50%	5 (5–7)
Prevent one hospitalization for exacerbation	57 (52–98)
Enable one patient to rate his/her asthma in good or excellent control	5 (4–6)

have previously shown no relationship between lung function and hospital admissions (Qureshi et al. 1998) as well as poor relationships between lung function and health-related quality of life (Wijnhoven et al. 2001). The most impressive benefit of omalizumab observed in the trials has been reduction in frequency of hospitalizations, where it reduced hospitalizations by 93.6% compared with placebo during the 12–16 weeks of the extension phase in three trials (1/767 omalizumab vs. 13/638 placebo; $p = 0.003$) (Busse et al. 2001; Milgrom et al. 2001; Soler et al. 2001; Avila 2007).

2.5.4 Impact of Omalizumab on Health-Related Quality of Life

An important secondary outcome in the studies, and one that is obviously of primary importance to the clinician, is improvement in heath-related quality of life. Traditionally, most studies in asthma have not focused on this aspect of outcome, rather focusing on conventional measurements of airway function such as spirometry, symptoms, medication usage, and degrees of airway hyperresponsiveness. Yet it is widely known that asthma exerts profound and variable effects on quality of life, and that such effects may be missed by measuring only conventional outcomes (Juniper 1999). Over the last two decades, the development and validation of several disease-specific instruments designed to assess quality of life have been developed. Moreover, these questionnaires are now widely available, easy to complete in 5–10 min, and found in multiple languages (Buhl 2003). Among the most widely used is the Asthma Quality of Life Questionnaire (AQLQ) (Juniper et al. 1992), a 32-item questionnaire that seeks to identify four basic domains in which asthma impacts one's quality of life: activity limitations, emotions, symptoms, and exposure to environmental stimuli. Each question is answered by the patient on a 7-point scale, from 1 (extremely impaired) to 7 (no impairment). Results are generally expressed in terms of a mean score for each domain, along with an overall score. An increase in domain or overall score of 0.5 or greater is generally accepted as clinically significant, and differences of 1.5 or greater reflecting a large improvement (Hajiro and Nishimura 2002; Jones 2002).

Initially, it appeared that use of omalizumab resulted in substantial improvement in health-related quality of life. This was evident by two of the four main clinical trials (Busse et al. 2001; Soler et al. 2001); these two studies not only utilized the AQLQ, but their similarities in study design allowed pooling of the data. Overall, patients treated with omalizumab experienced clinically relevant improvements in their asthma-related quality of life, as shown by improvements in mean scores of ≥ 0.5 in all four domains of the AQLQ, as well as the overall score (Buhl 2003). However, when more recent data were included in the analysis and the results pooled by the Cochrane Collaboration, the administration of subcutaneous omalizumab did not reach 0.5 (Walker et al. 2006), raising doubts about the significance of improvements in quality of life measures described above. Currently, it is still unclear as to what degree omalizumab improves quality of life measures in patients with asthma.

2.5.5 Summary of Efficacy in Asthma

Overall, the reduction in daily inhaled steroid use following treatment with omalizumab was modest but significant. However, the baseline steroid doses, the impressive effects of placebo treatment, and the mean difference in steroid consumption between treatment and placebo, bring in to question the true size of the steroid-sparing effects of omalizumab (Walker et al. 2006). An important caveat to the clinical trial data published so far is that, generally speaking, the majority of the data pertained to mild and moderate asthmatic subjects. Given that omalizumab

is generally used to treat patients with severe or difficult-to-treat asthma, it has not been studied as extensively in this population. Therefore, several investigators have formed a consortium known as The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) to study the natural history of such patients and the effects of advanced therapies such as omalizumab (Dolan et al. 2004).

2.5.6 Non-Asthma Atopic Diseases

In atopic diseases related to asthma, and specifically related to IgE, omalizumab has proven safe and effective. It attenuates early and late responses to allergen challenge to the skin (Beck et al. 2004; Ong et al. 2005) and early response to nasal allergen challenges (Kuehr et al. 2002) (late responses were not assessed). The magnitude of these reductions ranged from 20% to 70%. In addition, these reductions were associated with concomitant attenuation in local inflammatory diseases. It has been successfully used to treat allergic rhinitis alone and in combination with immunotherapy (Parks and Casale 2006). Recently, pretreatment of rush immunotherapy with omalizumab was found to decrease severity of anaphylaxis during therapy as well as decrease symptoms of ragweed-induced allergic rhinitis (Casale et al. 2006). Further clinical studies are needed in the use of omalizumab in the treatment of other atopic diseases such as atopic dermatitis, urticaria, and food allergies. Indeed, if omalizumab can control comorbid atopic conditions, this may be of particular benefit to asthmatic subjects who suffer from these related conditions; such benefit may, in some instances, justify the current high costs associated with the medication's administration.

2.6 Adverse Events and Safety Issues of Omalizumab

Omalizumab has so far been deemed to be a relatively safe medication, though information from phase IV trials are lacking in published form. The overall rate of any side effects in the phase III clinical trials was 80% for omalizumab-treated subjects and 77% for placebo-treated subjects, with injection-site reactions (45% treated, 43% placebo), viral infections (23% treated, 26% placebo), and upper-respiratory infections (20% treated, 20% placebo) accounting for the vast majority of these effects (Walker et al. 2006). Injection-site reactions were generally mild and included pain, induration, erythema, warmth, burning sensation, and localized hive formation.

Serious side effects occurred at similar rates between groups treated with omalizumab vs. placebo, yet particular concern is given to the development of anaphylaxis and malignancy. Anaphylaxis occurred in three subjects within 2 h of omalizumab injections, but none in the placebo arms (Genentech-Inc 2003; Rieves 2003). One patient developed large injection-site edema and mild pharyngeal edema. Another developed urticaria, skin pruritus and dyspnea hours after the initial treatment

(Avila 2007). Events resolved with epinephrine injections, oral antihistamines, and systemic corticosteroid administration. These reactions obviate the need for the ability to treat anaphylaxis in facilities that administer omalizumab. Moreover, the delayed anaphylaxis requires that patient and/or parent education be provided to recognize signs and symptoms of anaphylaxis.

There was a slightly increased risk of malignancy in patients treated with omalizumab, though this did not reach statistical significance. Malignancies occurred in 20 out of 4,127 (0.5%) of omalizumab-treated subjects and in 5 out of 2,236 (0.2%) of placebo-treated subjects (Genentech-Inc 2003; Rieves 2003; Avila 2007). In the omalizumab group, subjects were diagnosed with nonmelanoma skin cancer (5 subjects; one of these also had melanoma), breast cancer (5 subjects), prostate cancer (2), melanoma (2), parotid cancer (2), bladder cancer (2), non-Hodgkins lymphoma (1), pancreatic cancer (1), rectal cancer (1), and thyroid cancer (1). In the placebo group, subjects were diagnosed with nonmelanoma skin cancer (3 subjects), glioma (1), and testicular cancer (1). When expressed as events per exposure, there were 6.3 malignancies per patient-year in the omalizumab group and 3.3. in the placebo group for a rate difference of 3.0 and a rate ratio of 1.9 cancers per patient-year, both of which are not statistically significant. Moreover, the rate of cancer in the omalizumab group was similar to the expected rate for subjects of similar age and gender according to the National Cancer Institute's Surveillance, Epidemiology, and End Results database, which collects cancer statistics from 14% of the US population (Genentech-Inc 2003). Nevertheless, due to this heightened concern, Genentech has initiated the Epidemiologic Study of Xolair in Patients with Moderate to Severe Asthma (EXCELS) study and other surveillance evaluations to assess the natural medical history of patients with severe asthma, including rates of malignancies (Dolan et al. 2004; Borish et al. 2005; Slavin et al. 2006).

The development of immune complex disease and deposition seems to be a theoretical concern for many antibody-based therapies (Dillman 1989). If immune complexes are large, deposition can occur in multiple body tissues especially synovial joint spaces, the renal parenchyma, skin, and gastrointestinal tract. However, the humanization of the monoclonal antibody has resulted in less than 5% of amino acids being of murine origin, making the molecule less immunogenic. Moreover, if antibodies do develop, the resulting complexes are generally small and of low serum concentration (Liu et al. 1995). Among 1,723 subjects exposed to omalizumab, only one subject, who received the drug by inhalation, developed antibodies to omalizumab; none developed immune complex disease (Fahy et al. 1999). Overall, this appears to be less of a concern than was previously thought, but long-term data are not available as yet to clearly delineate this issue.

Though omalizumab has been studied and approved by the FDA for use in adolescents and adults, there are limited data in children under the age of 12, elderly subjects, and pregnant and nursing women. The latter issue deserves particular attention. In monkeys, omalizumab given at 12 times the dose used in clinical trials did not cause maternal toxicity, embryotoxicity, or teratogenicity. In human studies, 17 subjects became pregnant while receiving omalizumab, of whom 11 had normal deliveries and the others had spontaneous (3) or elective (3) abortions. In

the placebo group, 10 subjects became pregnant, of whom 6 had normal deliveries, 2 had spontaneous abortions, and 2 had unknown outcomes (Avila 2007). Omalizumab was stopped as soon as pregnancy was noticed. Though the FDA classified omalizumab as a category B drug for use in pregnancy, as an IgG1 molecule, omalizumab can cross the placenta and its effects are unknown. Therefore, at the time of this writing, we advise that omalizumab be stopped in the event of pregnancy.

Another safety concern for anti-IgE therapy is a theoretical risk of increased parasitic infections in patients treated with omalizumab. Parasitic infections result in increased IgE, though it is unclear if this effect is protective or simply a secondary marker of active parasite infection (Mingomataj et al. 2006). To test this hypothesis, anti-IgE-treated mice were infected with *Nippostrogylus brasiliensis* (Amiri et al. 1994). In this model, omalizumab treatment resulted in decreased worm load and enhanced parasite clearance. A related concern is that anti-IgE therapy, by affecting the body's response to parasitic infections, especially early in life, may modulate the development of asthma and atopy (Yazdanbakhsh et al. 2001). These concerns are not well-answered at this timepoint, especially given that published clinical trials to date have occurred in well-developed countries, where the incidence of parasitic infections remains low in comparison to lesser-developed regions.

Overall, it appears that administration of omalizumab appears relatively safe, especially when administered by a skilled staff that is able to recognize and treat anaphylaxis immediately. However, phase IV clinical trial data are needed, especially if anti-IgE therapy is to be continued lifelong.

2.7 Practical Aspects of Omalizumab

Despite the improvements seen in asthma exacerbations and quality of life with omalizumab, the exact role of omalizumab in clinical practice has yet to be defined (Avila 2007). As discussed earlier in the chapter, a number of pharmacologic, environmental, and possibly immunologic treatment options exist. Moreover, recently a number of studies have advocated the use of adjunctive therapies or focus on coexisting conditions (Roberts et al. 2006), such as allergic rhinitis and sinusitis (Dixon et al. 2006), gastroesophageal reflux disease (Harding 2005), vocal cord dysfunction (Jain et al. 2006), obesity (Chinn 2006), and obstructive sleep apnea (Yigla et al. 2003). Although national guidelines for asthma management have been in place and advocated for several years, it is clear that adherence to these guidelines is suboptimal (Reeves et al. 2006). Therefore, many critics of omalizumab feel that if commonly used treatment options are implemented that conform to national guidelines and coexisting conditions are managed effectively, many patients with moderate to severe asthma would be symptomatically well-controlled. This is particularly evident in the impressive placebo responses noted in the above-described trials. Although placebo effects have been observed with virtually any medication, it is likely that with asthma particular attention to peak flow measurements, education about inhaler usage and techniques, and prompt treatment of disease exacerbations

likely led to a strong placebo response. Given the suboptimal compliance observed in asthma medications, this could be seen as an advantage for omalizumab – a treatment that is administered periodically under clinical supervision has obvious benefits in this regard.

Despite the above criticisms, it is clear that better care is needed for the large number of patients with allergic asthma who are refractory to current therapies. What is not clear is which patients would specifically benefit from omalizumab. Patients who are particularly likely to benefit include those with evidence of sensitization to perennial aeroallergens who require high doses of inhaled corticosteroids and those with frequent exacerbations. Analyses of pooled data from published clinical trials have indicated that patients who had a response to omalizumab had a ratio of observed to expected FEV1 of less than 65% (normal $\geq$70%), were taking doses of inhaled corticosteroids equivalent to more than 800 mcg of beclomethasone diproprionate per day, and had had at least one visit to the emergency department in the past year (Bousquet et al. 2004; Bousquet et al. 2005). In general, current asthma symptoms are not a contraindication to the administration of omalizumab.

Dosing of omalizumab was discussed earlier and follows the normogram depicted in Table 1. A pretreatment total IgE is required, and dose adjustment made on the recommendation of 0.016 mg kg^{-1} of body weight per international unit of IgE. The drug is supplied as a lyophilized, sterile powder in single-use, 5-ml vials designed to deliver either 150 or 75 mg on reconstitution with sterile water for injection. The powder requires 15–20 min or more to dissolve, and the resulting viscous solution takes several seconds to both draw into the syringe and subsequently inject. Once prepared, the drug must be used within 4 h at room temperature or 8 h if refrigerated. Since doses can require several vials to be drawn and injected, the staff and facility demands for routine omalizumab injections can be beyond the capabilities of many clinicians' offices (Marcus 2006). From a subspecialty perspective, administration of omalizumab has been easier for allergists than pulmonologists for several reasons: (1) allergen skin testing (a requirement for administration of omalizumab) is routinely done in an allergist's office; (2) allergist offices routinely have patients do walk-in subcutaneous injections as done for immunotherapy; (3) allergists' staff are trained to quickly treat anaphylaxis (Marcus 2006; Avila 2007).

Omalizumab is considerably more expensive than conventional asthma therapy. At present, the cost of a single 150 mg vial is approximately $470, and accordingly yearly costs range from $6,100 to $36,600 per year (Marcus 2006). This compares with approximate annual costs of $1,280 for montelukast (Singulair, Merck), $2,160 for the combination of fluticasone diproprionate and salmeterol (Advair, GlaxoSmithKline), and $680 for extended-release theophylline (e.g., Uniphyl^{TM}) (Strunk and Bloomberg 2006). Given the expense, it is not surprising that many third-party payers are carefully surveying usage of omalizumab and that occasionally the approval process from Medicare and other payers may involve substantial administrative responsibilities (Marcus 2006). The only currently available cost-effectiveness analysis of omalizumab was limited to direct payer's costs and did not take into account indirect costs (Oba and Salzman 2004). The authors concluded that omalizumab is cost-effective in asthmatic subjects who experience $\geq$5

hospitalizations or ≥20 inpatient days for exacerbations per year. Clearly, a real-world cost-effectiveness analysis needs to be performed which accounts for not only direct and indirect costs of omalizumab administration, but also the health and societal effects of asthma control in patients optimized on various forms of asthma therapy.

Monitoring of total serum IgE levels during the course of therapy with omalizumab in not indicated, because these levels will be elevated as a result of the presence of circulating IgE-anti-IgE complexes. To date, free serum IgE levels are not routine and are prohibitively expensive for most laboratories. It is unclear if monitoring the free, circulating levels will have an effect on patient treatment and response, though assays are being investigated and developed for commercial availability and more widespread use.

3 Anti-TNF-α Therapy for Asthma

3.1 Role of Tumor Necrosis Factor-Alpha (TNF-α) in Asthma Pathogenesis

Tumor necrosis factor alpha (TNF-α) is an important cytokine in asthma pathogenesis. Extensive genetic, biologic, and physiologic evidence indicates that TNF-α may play a critical role in the initiation and amplification of airway inflammation in patients with asthma (Erzurum 2006). Preformed TNF-α is stored by mast cells and rapidly released during IgE-mediated reactions that typify the asthmatic response to allergens (Howarth et al. 2005; Mukhopadhyay et al. 2006) (Fig. 1). Elevated levels of TNF-α have been observed in induced sputum from patients with asthma (Keatings et al. 1997); moreover, the expression of TNF-α in asthmatic airways correlates with asthma disease severity (Howarth et al. 2005). Interestingly, inhalation of TNF-α by normal individuals increased airway responsiveness and neutrophil counts in induced sputum (Thomas et al. 1995) and TNF-α inhalation in patients with mild asthma causes airway hyperresponsiveness and sputum neutrophilia and eosinophilia (Thomas and Heywood 2002). TNF-α is a known candidate gene for asthma (Ober and Hoffjan 2006), and polymorphisms of the gene may be associated with the development of childhood asthma (Li et al. 2006).

Although it is clear that TNF-α is involved in asthma pathogenesis, the exact manner in which TNF-α effects its responses is complex and multifaceted. Macrophage activation in the late asthmatic response has been known to be a key pathway (Gosset et al. 1991), but TNF-α also upregulates adhesion molecule expression and activity, which leads to increased migration of eosinophils and neutrophils into the airways (Ohkawara et al. 1997). Airway epithelial cells are also activated by TNF-α to release cytotoxic mediators and reactive nitrogen and oxygen species that result in airway injury (Bayram et al. 2001; Bosson et al. 2003). The end result of chronic, unresolved inflammation is a structural change in the airway, termed airway remodeling. TNF-α may contribute to all aspects of remodeling, including the

proliferation and activation of fibroblasts, the increased production of extracellular matrix glycoproteins, subepithelial fibrosis, and mucous-cell hyperplasia (Erzurum 2006). Independent of its effect on inflammation, TNF-α also has direct effects on bronchial hyperreactivity to methacholine and allergen (Pennings et al. 1998).

3.2 The Use of Anti-TNF Therapy in Asthma

Humanized anti-TNF-α monoclonal antibodies (infliximab, adalimumab) and soluble TNF receptor blockers (etanercept) have been developed and shown to be effective in other inflammatory diseases such as Crohn's disease (Hyams et al. 2000) and rheumatoid arthritis (Scott and Kingsley 2006). In a murine model of asthma, treatment with anti-TNF-α monoclonal antibodies reduces pulmonary inflammation and airway hyperresponsiveness, perhaps via a decrease in eotaxin levels (Kim et al. 2006). Over the past several years, a number of studies have been undertaken to evaluate the potential benefits of anti-TNF therapy in diseases such as asthma (Howarth et al. 2005; Berry et al. 2006; Erin et al. 2006), chronic obstructive pulmonary disease (van der Vaart et al. 2005), and other diseases of lung and airway injury (Mukhopadhyay et al. 2006).

In a UK study, 17 subjects with severe corticosteroid-dependent asthma were administered subcutaneous etanercept (Enbrel™, Wyeth Laboratories, Berkshire, UK) in an open-label fashion and assessed for clinical and biological response. Administration of etanercept was associated with improvement in asthma symptoms, lung function, and bronchial hyperresponsiveness (Howarth et al. 2005). These effects were maintained 2–4 weeks after cessation of therapy, after which the benefits were lost. This trial prompted a follow-up study in which 10 patients with refractory asthma were randomized to etanercept in a crossover pilot study (Berry et al. 2006). In this study, 10 weeks of treatment with etanercept was associated with a significant improvement in methacholine responsiveness, asthma-related quality of life score, and post-bronchodilator FEV1.

Recently, another study was published investigating the usage of a different anti-TNF agent, infliximab (Remicade™, Centocorp Inc., Malvern, PA, USA). In this study, 38 patients with moderate-to-severe persistent asthma currently being treated with inhaled corticosteroids, were randomized to treatment with intravenous infliximab or placebo (Erin et al. 2006). Infliximab was well-tolerated and associated with a decrease in mean diurnal variation of peak expiratory flow (a marker of airway obstruction) and fewer numbers of patients with asthma exacerbations among the treated group. Concordantly, there were lower levels of TNF-α and other inflammatory markers in the sputum of treated subjects. Importantly, there were no treatment-related statistically significant effects of morning peak expiratory flow, exhaled nitric oxide levels, or blood or sputum eosinophilia. This was merely a pilot study, and larger studies are needed to understand the effects of TNF-α inhibition in asthmatics.

3.3 Additional Issues Regarding Anti-TNF Therapy in Asthma

The above data regarding the usage of anti-TNF therapies for asthma are quite preliminary as the number of study subjects are small and larger controlled trials are needed. Injection site reactions were common with administration of infliximab and etanercept, but were mild and easily treated.

The greatest concern in the use of these antibody-mediated therapies is the potential risks for acquiring serious infections. Animal studies have long shown an essential role of TNF-α in fighting infection; therefore, suppression of this arm of host defense may significantly hamper one's ability to fight pathogens. Serious infections with anti-TNF therapies have been associated with all the anti-TNF therapies to date (Giles and Bathon 2004). These can be either usual bacterial infections (Kroesen et al. 2003), but may also include tuberculosis (Keane et al. 2001; Bresnihan and Cunnane 2003), serious fungal infections (Wood et al. 2003), and other less-commonly seen pathogens. It is perhaps the alarming incidence of tuberculosis that has most healthcare workers concerned about the use of anti-TNF therapies, as disease has great public health and treatment-related consequences (Rychly and DiPiro 2005). Recently, a systematic review was published addressing this concern – 9 clinical trials of over 3,900 patients with rheumatoid arthritis treated for 12 weeks or longer with anti-TNF therapies were compared to 1,512 patients who received placebo (Bongartz et al. 2006). In patients treated for 3–12 months, the odds ratio for serious infections in the treated group was 2.0 (95% CI 1.3 to 3.1), meaning essentially double the incidence of serious infections in the treated group vs. control group. The incidence of serious infection was almost 1 in 60 treated subjects based upon this analysis. This is not as high as others would have predicted, but is still clinically relevant.

Another important concern in the use of anti-TNF therapies is the theoretical increased incidence in the development of malignancy. TNF was originally named for the recognition of its ability to kill tumor cells in vitro and is important in natural killer cell and CD8 lymphocyte-mediated killing of tumor cells. In the above-mentioned meta-analysis by Bongartz et al., the pooled odds ratio for the development of malignancy in these patients with rheumatoid arthritis was 3.3 (95% CI 1.2–9.1), and the authors estimated that roughly one malignancy would develop for every 154 patients treated with anti-TNF therapies (treatment period of 3–12 months). Moreover, this is dose-dependent as studies utilizing higher doses were associated with greater incidences of malignancy formation.

Other potential adverse effects associated with anti-TNF therapies include the development of congestive heart failure, demyelinating diseases, and systemic lupus erythematosus, but in most cases these can be identified and managed (Hochberg et al. 2005). As an aside, adalimumab was associated, paradoxically, with the development of asthma in a single case report (Bennett et al. 2005), though the mechanism for this remains speculative.

Overall, anti-TNF therapies are important in the treatment of many immunologically mediated diseases, though their roles in asthma remain uncertain as yet given the paucity of clinical data. Needless to say, more data are needed to gain better understanding of potential benefits in patients with asthma. Moreover, concerns for infection, malignancy, and other serious adverse effects remain particularly important in the evaluation of these therapies. Like anti-IgE therapy, anti-TNF therapies share many concerns for parenteral administration, costs, and identifying patients who would most benefit from these therapies.

4 Other Antibody-Mediated Therapies for Asthma

There are numerous other potential antibody targets in asthma (Walsh 2005; Walsh 2006). Since much asthmatic inflammation is thought to be a consequence of uncontrolled inflammation, it follows that a number of targets are being developed that modulate inflammatory pathways.

4.1 Antibodies to Interleukin-5

Interleukin-5 (IL-5) is a cytokine that is crucial to the development and release of eosinophils and the subsequent release of eosinophils from the bone marrow, their enhanced adhesion to endothelials cells lining the postcapillary tissues. Several animal models of asthma, including primates, have provided good evidence that inhibiting the effects of IL-5 using specific monoclonal antibodies inhibited eosinophilic inflammation and airway hyperresponsiveness. Given its central role in regulating eosinophil development and function, IL-5 was therefore chosen as a potentially attractive target to prevent or blunt eosinophil-mediated inflammation in patients with asthma.

To date, clinical trials with anti-IL5 monoclonal antibodies have not reported substantial efficacy. The first study of mepolizumab (Leckie et al. 2000) was criticized for lack of power and validity of patient selection. A later placebo-controlled study found that treatment of mild asthmatic patients with mepolizumab abolished circulating eosinophils and reduced airway and bone marrow eosinophils (Flood-Page et al. 2003b); however, there were no significant improvements in clinical measures of asthma. Interestingly, lung biopsy samples from the treatment group contained intact tissue eosinophils and large quantities of eosinophil granule proteins, likely explaining the lack of clinical benefit. Similar findings were reported with the anti-IL5 monoclonal antibody SCH55700 in patients with severe asthma that had not been controlled by inhaled corticosteroid use (Kips et al. 2003). These authors reported profound reductions in circulating eosinophils, but no significant improvement was observed in either asthma symptoms or lung function. Interestingly, anti-IL-5 therapy reduced deposition of extracellular membrane proteins in

the bronchial subepithelial basement membrane of mild allergic asthmatics, hence implying that this therapy may improve airway remodeling in asthma (Flood-Page et al. 2003a).

4.2 Antibodies to Interleukin-4 and Interleukin 13

Another cytokine important in eosinophil accumulation is Interleukin-4 (IL-4), and together with its close relative, Interleukin-13 (IL-13), it is important in IgE synthesis by B cells. Both cytokines signal through a shared surface receptor, IL-4α, which then activates the transcription factor, STAT-6 (Jiang et al. 2000). Studies with soluble IL-4 given in a nebulized form demonstrated that the fall in lung function induced by withdrawal of inhaled corticosteroids was prevented in patients with moderately severe asthma (Borish et al. 2001). However, despite these promising findings, subsequent trials have not been as successful and consequently this treatment is no longer being developed (Walsh 2005). Other approaches for blocking the IL-4 receptor include administration of antibodies against the receptor and mutant IL-4 proteins. Interrupting IL-4 receptor signaling by targeting transcription factors such as STAT-6, GATA-3, or FOG-1 might also be possible (Barnes 2003).

IL-13 has been found in bronchoalveolar lavage fluid following allergen provocation of asthmatic subjects, which strongly correlated with the increase in eosinophil numbers (Kroegel et al. 1996) and mRNA expression was detected in bronchial biopsies from allergic and nonallergic asthmatic subjects (Humbert et al. 1997). In animal models, IL-13 mimics many of the pro-inflammatory changes associated with asthma (Grunig et al. 1998). Two receptors for IL-13 have been described – IL-13Rα1 and IL-13Rα2. The latter exists in soluble form and has a high affinity for IL-13, which by competitive inhibition of IL-13 results in decreases in IgE production, pulmonary eosinophilia, and airway hyperresponsiveness (Wills-Karp et al. 1998). A humanized IL-13Rα2 is in clinical development as a novel therapy for asthma, but results so far have been inconclusive about its benefits (Walsh 2006).

4.3 Other Antibody-Based Therapies in Development

A number of potential antibody-mediated therapies are probably worth mentioning but beyond the scope of this chapter, as data are too preliminary on their potential for clinical effectiveness. The majority of these therapies invariably involve control of the inflammatory cascade. The spectrum of potential sites of action is diverse, and may involve targeting of intracellular adhesion molecules located on inflammatory cells and airway epithelia (e.g., VCAM), specific therapies against mast cells and their mediators (e.g., tryptase, prostaglandins), regulation of apoptosis of inflammatory cells (e.g., via inhibition of NF-κB), regulation of cell cycling and signaling

cascades, and even gene-based therapies that target transcriptional activation of the inflammatory cascade (Walsh 2005).

5 Summary

Asthma remains a disease of great public health importance, and though current therapies have dramatically improved asthma control in the vast percentage of patients with asthma, current treatments remain inadequate in certain segments of the asthma population. Antibody-mediated therapies, specifically anti-IgE therapy, are proving to be viable tools in the management of asthma and related inflammatory disorders. Though their current roles are still being determined, and long-term efficacy and safety data still being accumulated, we believe that such targeted therapies will ultimately change the daily management of asthma.

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